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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,503	03/04/2005	Akira Suzuki	05273.0096-00000	9248

22852 7590 10/05/2006

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
RAZA, SAIRA B	

ART UNIT	PAPER NUMBER
1711	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/526,503	SUZUKI ET AL.	
	Examiner	Art Unit	
	Saira Raza	1711	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The rejections have been maintained.

Claim Rejections - 35 USC § 102

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1-7, 15, 16, 18-20, 22 rejected under 35 U.S.C. 102(b) as being anticipated by Thanoo et al. (US 6,270,802) (Column: Lines:: 1:20-50, 2:6-10, 3:11-66, 4:11-17, 4:38-59, 5:30-57, 6:3, 7:1-30, 11:30-65, Example 1, Claims 1 19).

4. From a Prior Office Action:

5. In reference to claims 1 and 18, Thanoo discloses a process for making microspheres comprising: Preparation of the dispersed and continuous phases and feeding the phases to a reaction vessel in which the dispersed phase is interspersed or emulsified to form droplets in the continuous phase. Attention is directed towards US 5,945,126 which is incorporated into US 6,270,802 by reference. (See US 5,945,126 at Column: Lines:: 4:25 to 5:15, 6:38-50, 7:47-54, Example 1). The '126 reference discloses details regarding the phases; the dispersed phase comprises a polymer, an active agent (drug) and a solvent. Specifically, the polymer is biocompatible, biodegradable, and hardly-water soluble. The organic solvent has a boiling point lower that that of water and the continuous phase is an aqueous solution.

6. Thanoo in the '802 reference states that the emulsion is then transported from the reactor vessel into a holding tank (**24** in Figure 1) and then into a formulating vessel (i.e. microsphere storage tank) (**16** in Figure 1).

7. A portion of the emulsion in the formulating vessel is pumped to a filter. Thanoo states "Conceptually, any filter that is adapted to eliminate continuous phase and return the polymer bodies [microspheres] as a suspension to a process vessel [**16** in Figure 1] will suffice for the practice of the invention, with the noted hollow fiber filter being preferred." Hence Thanoo would envisage utilization of a cross flow filter.

8. The filtration process of Thanoo has two outward streams, the filtrate (the continuous phase) and the retentate (the suspension of microspheres). The filtrate is removed by the filter and transferred to a waste tank. The suspension passes through the filter and is transferred back to the formulation vessel (**16** in Figure 1).

9. The formulating vessel also functions as a solvent evaporation tank wherein the residual solvent is evaporated. The microspheres are collected in the formulation vessel. The entire process above is repeated. Wherein it is inherent that a fresh aqueous solution (continuous phase) is utilized in the formation of the emulsion, since Thanoo has not stated recycling of the continuous phase.

10. In reference to claim 2, the dispersed phase, containing the drug, polymer and solvent, is, as per the '126 reference, a solution in which the polymer and drug are dissolved in the organic solvent.

11. In reference to claims 3-4, the emulsification can be carried out either continuously or batch-wise, and the resulting emulsion is either continuously or batch-wise transferred into the holding tank.

12. In reference to claim 5-6, Thanoo discloses that the organic solvent is evaporated from the emulsion in the formulation vessel by warming and/or with a hollow fiber filter.

13. In reference to claims 7 and 19, Thanoo discloses that a suitable organic solvent is methylene chloride, a halogenated aliphatic hydrocarbon, and in the '126 reference the polymer is polylactic acid, a polyester of a hydroxyfatty acid.

14. In reference to claim 15, the '126 reference discloses that the emulsification is carried out with an impeller type apparatus, a flow restriction device that forces the continuous and dispersed phases through progressively smaller channels causing highly turbulent flow, a high frequency sonication tip or similar apparatus that will be apparent to those of ordinary skill in the art in view of this disclosure. The '126 reference requires that the dispersed and continuous phases are mixed under high shear force, and a few of the devices mentioned utilize liquid-liquid shear.

15. In reference to claim 16, the '126 reference discloses that the ratio of the continuous phase and dispersed phase is from 5:1 to 500:1.

16. In reference to claim 20, the microcapsules are collected by hollow fiber filtration.

17. In reference to claim 22, Thanoo discloses that the microspheres from the process of claim 1 are freeze dried (lyophilized).

Claim Rejections - 35 USC § 103

18. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

19. Claims 8-14, 17, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thanoo et al. (US 6,270,802).

20. From a Prior Office Action:

21. In reference to claims 8 and 9, Thanoo discloses via incorporation of the '126 reference, that a suitable organic solvent includes acetone. Since the organic solvent and water are miscible, it would be obvious to one of ordinary skill in the art at the time of the invention that the organic solvent would be part of the aqueous continuous phase and would be removed during the filtration process; hence evaporation in the formation vessel would not be required.

22. In reference to claim 10, the '126 reference discloses that solvents used to dissolve the active agent (drug) into the dispersed phase will vary depending on the nature of the agent, and that solvents for the polymer will also vary depending upon a number of factors, including the nature of the polymer active agent, toxicity, and compatibility with the other solvents in the system. The '126 reference further discloses that the solvent of the dispersed phase must be immiscible with the continuous phase in order to form droplets. The '126 reference discloses that the aqueous based continuous phase contains a solvent such as PVA, which functions as a stabilizer and is inherently immiscible with the selected organic solvent of the dispersed phase. The organic solvents of both the dispersed and aqueous continuous phase meet the limitations of claim 10. It would have been obvious to one of ordinary skill in the art at the time of the invention to have included a solvent in the continuous phase that is immiscible with the dispersed phase in order ensure that droplets would form in the emulsion. Wherein the ingredients of both the continuous and dispersed phases inherently meet all of the limitation of claim 10.

23. In reference to claim 11, Thanoo fails to disclose the filtration speed though the cross flow filter and emulsion influx speeds from the emulsifying device as claimed. Thanoo discloses that various pumps are utilized to control the speed of various input and output fluids. It would have been obvious to one of ordinary skill in the art at the time of the invention to control the filtration and emulsion influx speed in the process of Thanoo in order to maintain a certain emulsion volume in the formulation vessel and prevent overflow or drying-out in the formulation vessel.

24. In reference to claim 12, Thanoo fails to disclose that the capacity of the formation vessel is 10 –1000 times that of the emulsifying device for batch-treatment. It would have been obvious to one of ordinary skill at the time of the invention to have a storage tank, which is at least 10 times greater than the emulsifying device in order to ensure that the storage tank is capable of containing

at least 10 batches of the emulsion. Additionally, the size of the tanks is an adjustable feature which an artesian skilled in the art would readily be capable of altering to achieve the intended purpose.

25. In reference to claims 13 and 14, Thanoo fails to expressly disclose the pore size of the cross flow filter, although Thanoo envisages employment of the filter. The hollow fiber filter that Thanoo utilizes has a pore size of 0.45μm. It would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized a cross flow filter with a pore size of 0.45μm in order to obtain microcapsules with a size greater than 0.45μm and eliminate particles smaller than 0.45μm. In reference to speed at which the emulsion is introduced and the filtrate removed, Thanoo states that, "with the preferred filter, the rate at which continuous phase is removed by the filter should not exceed about one third of the flow rate of continuous phase through the filter, otherwise flow and clogging problems can occur." It would have been obvious to one of ordinary skill at the time of the invention to have adjusted the filtration speed of the filtrate from the cross flow filter to 1/3 of the introduction speed of the emulsion into the filter in order to possibly avoid flow and clogging problems. Only a reasonable expectation of success, not absolute predictability is necessary for obviousness. *In re Longi*, 759F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985). An expectation is reasonable if one of ordinary skill in the art would have considered it "logical to anticipated with a high degree of probability that a trial of the modification of the filtration speeds and pore size would have been successful." *In re Pantzer*, 341 F2d. 121, 126;144 USPQ 415, 419 (CCPA 1965).

26. In reference to claims 17 and 21, Thanoo fails to disclose that the filtrate (the continuous phase) is recycled and used in the emulsion step, and he fails to disclose that the medicament/drug is recovered from the aqueous solution after collection of the microspheres. It would have been obvious to one of ordinary skill in the art at the time of the invention to instead of sending the

filtrate to the waste to have recycled it and extracted any remaining drug. The motivation would be to salvage expensive drugs and reuse the sterile continuous phase to form the emulsion.

Response to Arguments

27. Applicant's arguments filed 7/20/2006 have been fully considered but they are not persuasive.

28. Applicant argues that in the process of Thanoo, the already prepared microcapsules are passed through the filter, wherein applicant claims that the emulsion is passed through the filter. It is noted that Thanoo discloses that the suspension of solidified dispersed phase particles suspended in the continuous phase will generally be transferred to the tank **24**, wherein the polymer bodies being transferred to the tank **24** may not yet be solidified or otherwise may still be in the process of forming (col. 5, lines 33-39). Additionally, Thanoo discloses that the process vessel [**16** in Figure 1] includes a means for maintaining the polymer bodies in suspension therein; such means include magnetic stirrers, impellers, and the like (col. 6, lines 43-49). Thanoo does not explicitly disclose that 100% of the polymer bodies in the suspension are solidified; hence, some of the polymer bodies in the suspension may not yet be solidified, or otherwise still may be in the process of forming. Thus meeting the claimed limitations. It is noted that applicant does not claim the absence of microcapsule formation prior to filtration.

Conclusion

29. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Saira Raza whose telephone number is (571) 272-3553. The examiner can normally be reached on Monday-Friday from 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Seidleck can be reached on (571) 272-1078. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James J. Seidleck
Supervisory Patent Examiner
Technology Center 1700